(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
14 October 2004 (14.10.2004)

PCT

(10) International Publication Number
WO 2004/088361 A2

(51) International Patent Classification[7]: G02B

(21) International Application Number:
PCT/US2004/010152

(22) International Filing Date: 31 March 2004 (31.03.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

| | | |
|---|---|---|
| 60/459,543 | 31 March 2003 (31.03.2003) | US |
| 60/476,600 | 6 June 2003 (06.06.2003) | US |
| 60/514,769 | 27 October 2003 (27.10.2003) | US |

(71) Applicant *(for all designated States except US)*: **THE GENERAL HOSPITAL CORPORATION** [US/US]; 55 Fruit Street, Boston, MA 02114 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **TEARNEY, Guillermo, J.** [US/US]; 118 Kinnaird St., #3, Cambridge, MA 02139 (US). **IFTIMIA, Nicusor**. **BOUMA, Brett, E.** [US/US], 12 Monmouth St., Quincy, MA 02171 (US).

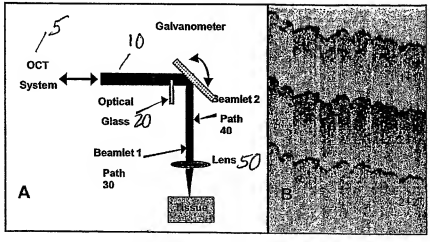
(74) Agent: **ABELEV, Gary**; Baker Botts LLP, 30 Rockefeller Plaza, New York, NY 10112-4498 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, BG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK,

*[Continued on next page]*

(54) Title: SPECKLE REDUCTION IN OPTICAL COHERENCE TOMOGRAPHY BY PATH LENGTH ENCODED ANGULAR COMPOUNDING




(57) Abstract: Speckle, a factor reducing image quality in optical coherence tomography ("OCT"), can limit the ability to identify cellular structures that are important for the diagnosis of a variety of diseases. The present invention allows for an implementation of an angular compounding, angular compounding by path length encoding ("ACPE") for reducing speckle in OCT images. By averaging images obtained at different incident angles, with each image encoded by path length, ACPE maintains high-speed image acquisition and implements minimal modifications to OCT probe optics. ACPE images obtained from tissue phantoms and human skin in vivo demonstrate a qualitative improvement over traditional OCT and an increased signal-to-noise ratio ("SNR"). Accordingly, apparatus probe catheter, and method are provided for irradiating a sample. In particular, an interferometer may forward forwarding an electromagnetic radiation. In addition, a sample arm may receive the electromagnetic radiation, and can include an arrangement which facilitates a production of at least two radiations from the electromagnetic radiation so as to irradiate the sample. Such arrangement can be configured to delay a first radiation of the at least two radiations with respect to a second radiation of the at least two radiations.

WO 2004/088361 A2

TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

**Published:**

— *without international search report and to be republished upon receipt of that report*

*For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

# SPECKLE REDUCTION IN OPTICAL COHERENCE TOMOGRAPHY BY PATH LENGTH ENCODED ANGULAR COMPOUNDING

## CROSS-REFERENCE TO RELATED APPLICATIONS

The present application claims priority from U.S. Patent Application Serial No. 60/459,543 filed on on March 31, 2003, International Patent Application No. PCT/US03/02349 filed on January 24, 2003, and U.S. Patent Applications Serial Nos. 60/476,600, 60/514,769, filed on June 6, 2003 and October 27, 2003, respectively, the entire disclosures of which are incorporated herein by reference.

## FIELD OF THE INVENTION

The present invention relates to optical imaging methods and apparatus useful in medical diagnosis and imaging. In particular, the present invention relates to a high speed method for implementing angular compounding, e.g., angular compounding by path length encoding ("ACPE") for reducing speckle in optical coherence tomography images.

## BACKGROUND INFORMATION

Optical coherence tomography ("OCT") is a technique for obtaining high resolution cross-sectional images of biological tissues. Clinical OCT studies conducted in the gastrointestinal tract and cardiovascular system have shown that OCT is capable of providing images of the architectural (>20μm) microanatomy of a variety of epithelial tissues, including the layered structure of squamous epithelium and arterial vessels. However, for certain medical applications, such as the early detection of high-grade dysplasia in Barrett's esophagus and the identification of inflammation within atherosclerotic plaques, visualization of structures that are on a size scale of < 20 μm may be preferable. OCT systems, with typical axial resolutions ranging from 8 - 12 μm, have the potential to resolve many of these structures, including nuclei, individual glands, and macrophages. Unfortunately, speckle, which occurs on the same size scale as these features, may prohibit unambiguous

including nuclei, individual glands, and macrophages. Unfortunately, speckle, which occurs on the same size scale as these features, may prohibit unambiguous identification of the cellular and subcellular tissue components required for widespread clinical utilization of such technology.

Catheter or endoscope access and high-speed imaging is used in order to perform OCT in the internal organs of patients. In order to minimize diameter, most catheter-based OCT probes employ a single optical fiber to illuminate the sample and detect the signal from the tissue. High frame rates (typically 4-10 frames per second) are preferred for performing OCT imaging while minimizing artifacts caused by patient motion. A way to reduce speckle in OCT images that does not significantly increase the complexity of single optical fiber probe designs while maintaining high frame rates may be beneficial for applying OCT to accurately detect and quantify key microscopic tissue structures in patients.

The reduction of speckle in the OCT images speckle has been previously described. A publication by J. M. Schmitt, "Array Detection for Speckle Reduction in Optical Coherence Microscopy," Phys. Med. Biol. 42, 1427–1429, 1997, the entire disclosure of which is incorporated herein by reference, describes a procedure for a speckle reduction by averaging multiple images acquired at different angles, known as angular compounding. In this publication, multiple ($N$) detectors receive images that have been acquired from different angles. The images are averaged incoherently, providing an improvement ($\sqrt{N}$) in the signal to noise ratio ("SNR"). While this technique has the advantage that the measurements may be performed in real-time, the experimental apparatus as described therein would not be compatible with a single fiber optic catheter.

Another publication, M. Bashkansky and J. Reintjes, "Statistics and reduction of Speckle in Optical Coherence Tomography," Opt. Lett. 25, 545–547, 2000, the entire disclosure of which is incorporated herein by reference, describes an alternative technique for angular compounding to reduce speckle. In this method, a retroreflector apparatus is translated in front of the objective lens to change the angle of the incident beam on the tissue. $N$ successive images are acquired and added incoherently to reduce speckle, again improving the SNR by a factor of $\sqrt{N}$. While this method may be less complex than the use of multiple detectors, the time needed thereby to acquire the images is increased by $N$. In addition, the implementation of

this method within the confines of a small diameter catheter or endoscope could be difficult.

## SUMMARY OF THE INVENTION

According to one exemplary embodiment of the present invention, a method for performing angular compounding to reduce speckle within OCT images is provided, which may use angular compounding by path length encoding ("ACPE"). With ACPE, a high-speed acquisition can be maintained, and modifications to standard OCT catheter optics are likely to be minimal. In another exemplary embodiment according to the present invention, an apparatus for imaging is provided that uses ACPE.

Accordingly, apparatus probe catheter, and method according to exemplary embodiments of the present invention are provided for irradiating a sample. In particular, an interferometer may forward forwarding an electromagnetic radiation. In addition, a sample arm may receive the electromagnetic radiation, and can include an arrangement which facilitates a production of at least two radiations from the electromagnetic radiation so as to irradiate the sample. Such arrangement can be configured to delay a first radiation of the at least two radiations with respect to a second radiation of the at least two radiations.

According to another exemplary embodiment of the present invention, a reference arm provides a further electromagnetic radiation. In particular, the interferometer receives the first, second and further radiations, and forms a resultant signal based on the first, second and further radiations. A processing arrangement may also be provided for generating a first image based on the first radiation and a second image based on the second radiation, such that the first and second images are different from one another. The further image may be generated based on the first and second images. In addition, the further image may have a noise that is smaller than a noise of the first image and a noise of the second image. Also, the further image may have a signal to noise ratio that is improved according to the equation:

$$SNR_{ACPE} = \frac{\langle S_{OCT} \rangle}{\sqrt{\mathrm{var}[S_{OCT}]}} \propto \frac{\sum_{i=1}^{N} u_i}{\sqrt{\sum_{i=1}^{N} u_i^2}},$$

where SNRACPE is the signal to noise ratio, SOCT is an amplitude of a high-pass filtered OCT signal, m is a thickness of the arrangement, ui is an amplitude of a demodulated OCT signal at a spatial location, and N = 2m - 1. Further, m=2 and N=3 images associated with the at least two radiations may be obtained. The further image may also be generated based on a mathematical combination of the first and second images.

According to yet another exemplary embodiment of the present invention, the sample can be irradiated by the first irradiation at a first angle, and by the second radiation at a second angle, such that the first and second angles different from one another. For example, the first and second angle may be different from one another based on the delay and at least one of a phase and a incident angle of each of the first and second radiations. It is also possible to utilize a detector which detects the first electromagnetic energy, and forwards the detected energy to the processing arrangement.

In still another exemplary embodiment of the present invention, the arrangement can include two sections, each being configured to delay a respective one of the first and second radiations. In particular, a delay of the first radiation is preferably greater than a delay of the second radiation. In addition, the delay of a path of the first radiation compared to a path of the second radiation is at least 500μm in air. Further, the delay of a path of the first radiation compared to a path of the second radiation is at least 1mm in air. The arrangement may have a refractive index of at least 1.5 or at least 3.0. The arrangement can include silicon and/or an anti-reflective coating on at least one surface thereof. Such arrangement can be an anti-reflection-coated BK 7 glass. The glass may have a thickness of from about 1.6 mm to about 7.7 mm, and a refractive index of from about 1.51 to about 3.5.

According to yet another exemplary embodiment of the present invention, an apparatus for imaging is provided. The apparatus includes a sample arm that receive an electromagnetic radiation. The sample arm includes an arrangement which facilitates a production of at least two radiations from the electromagnetic radiation so as to irradiate a sample. The arrangement is configured to delay a first radiation of the at least two radiations with respect to a second radiation of the at least two radiations. The apparatus also includes a device for receiving the first and second radiations from the sample arm and at least one third radiation from a reference arm,

such that the first and second radiations interfere with the third radiation. Further, the apparatus includes at least one of spectral separating unit which separates spectrum of at least one of the first, second and third radiations into frequency components, and at least one detection arrangement including a plurality of detectors. Each detector is capable of detecting at least a portion of at least one of the frequency components.

In a further exemplary embodiment of the present invention, an apparatus is provided. Such apparatus includes at least one first arrangement that provides at least one first electro-magnetic radiation to a sample arm and at least one second electro-magnetic radiation to a non-reflective reference arm. A frequency of radiation provided by the first arrangement varies over time. The sample arm receives the first electromagnetic radiation, and includes an arrangement which facilitates a production of at least two radiations from the electromagnetic radiation so as to irradiate a sample. The arrangement is configured to delay a first radiation of the at least two radiations with respect to a second radiation of the at least two radiations. The apparatus also includes at least one second arrangement detecting an interference between the first and second radiations generated at the sample arm and the second electro-magnetic radiations generated at the reference.

In still another exemplary embodiment of the present invention, an apparatus is provided. The apparatus includes a. at least one first arrangement providing at least one first electro-magnetic radiation to a sample arm and at least one second electro-magnetic radiation to a reference arm. The first and/or second electro-magnetic radiation have a spectrum which changes over time. The spectrum contains multiple frequencies at a particular time. The sample arm receives the first electromagnetic radiation, and includes an arrangement which facilitates a production of at least two radiations from the electromagnetic radiation so as to irradiate a sample. The arrangement is configured to delay a first radiation of the at least two radiations with respect to a second radiation of the at least two radiations. The apparatus also includes at least one second arrangement detecting an interference between the first and second radiations generated at the sample arm and the second electro-magnetic radiations generated at the reference.

Other features and advantages of the present invention will become apparent upon reading the following detailed description of embodiments of the invention, when taken in conjunction with the appended claims.

## BRIEF DESCRIPTION OF THE DRAWINGS

The invention is illustrated in the drawings in which like reference characters designate the same or similar parts throughout the figures of which:

Fig. 1A is a schematic diagram of an exemplary embodiment of an ACPE-OCT apparatus according to the present invention.

Fig. 2A is a schematic diagram of an exemplary embodiment of an Intralipid-Agar phantom according to the present invention.

Fig. 2B is an exemplary OCT image of the phantom of Fig. 2A without the insertion of a BK7 ACPE element.

Fig. 2C is an illustration of exemplary ACPE OCT images obtained by splitting a sample beam in two parts using an exemplary 3.1 mm BK7 glass element.

Fig. 3A is an exemplary OCT image of a ventral forearm obtained in vivo prior to the insertion of the BK7 ACPE element.

Fig. 3B is an exemplary compounded ACPE OCT image of the skin acquired at the same location as that in Fig. 3A.

## DETAILED DESCRIPTION

### I. Materials and Methods

Fig. 1A shows an exemplary embodiment of an apparatus according to the present invention which uses ACPE. An optical glass 20 is placed in an imaging path 10 of a conventional OCT imaging apparatus 5, splitting the incident field into two beamlets 1 and 2 which are provided on beam paths 30 and 40, respectively. For the purpose of the present discussion, a beamlet can be defined as a portion of a beam. An optical element (e.g., the optical glass 20) causes a portion of the incident beam (beamlet 2) to experience a greater path length delay than beamlet 1. In addition, beamlet 2 illuminates the sample at a different angle than beamlet 1. A lens may be provided to converge the beamlets 1 and 2 onto the sample (e.g., a tissue). As a result, multiple OCT images of a specimen in or on the sample, each acquired at a different angle, can appear simultaneously on the OCT display (see Fig. 1B). In particular, Fig. 1B shows that the top image (i.e., labeled as 1 + 1) corresponds to the image formed from path 1 (i.e., incident and reflected), the middle image (i.e., labeled

as 1 + 2, 2 + 1) corresponds to the image formed from path 1 incident, path 2 reflected and path 2 incident, path 1 reflected. Further, the bottom image (i.e., 2 + 2) of Fig. 1B corresponds to the image formed from path 2 (incident and reflected).

These beamlets 1 and 2, thus encoded by optical path length, also illuminate the sample at different angles. As a result, multiple OCT images, each acquired at different angles, are preferably present in a single OCT frame (as shown in Fig. 1B). For example, when the optical element contains *m* distinct thicknesses of glass, with each optical thickness a multiple of the others, *2m - 1* OCT images can be obtained in one OCT frame. Each image may be separated by a group delay of $D(n-1)/2$, where *D* is the thickness and *n* is the refractive index of the optical material. The distinct OCT images are then averaged to produce a composite OCT image with significantly reduced speckle. Since all of the images are acquired in one OCT frame, single frame acquisition time can be maintained. In addition, the modifications to the OCT probe may involve only the insertion of at least one small optical element in the beam path of the distal optics. These advantages of ACPE allow speckle averaging to be performed within the confines of a small diameter catheter or endoscope, and without compromising the acquisition speed.

Previous attempts of utilizing OCT speckle reduction by image compounding has shown that the addition of *N* images of the same intensity provides an SNR increase by a factor of $\sqrt{N}$. For example, the Bashkansky publication described above describes that the speckle distribution in OCT takes the form of the probability density function:

$$p(S_{OCT}) = \frac{1}{\sqrt{2\pi}\kappa}\exp\left(\frac{-S_{OCT}^2}{2\kappa^2}\right) \qquad (1)$$

where $\kappa = 2A_R\sigma$, with $A_R$ is the amplitude of the reference field, $S_{OCT}$ is the amplitude of the high-pass filtered OCT signal, and $\sigma$ is its standard deviation. For this probability density function, it can be demonstrated that the SNR improvement obtained by averaging *N* images of the same amplitude is also a factor of $\sqrt{N}$, a result that has been experimentally described in the Schmitt and Bashkansky publications. For ACPE, the distinct OCT subimages generally may not have equal amplitudes. However, with the assumption of isotropic backscattering, these subimages are related to the original OCT image, $S0_{OCT}$, by $\beta/m^2$, where $\beta$ is the

number of path length combinations that contribute to a distinct subimage. As a result, the SNR for ACPE may be defined as

$$SNR_{ACPE} = \frac{\langle S_{OCT} \rangle}{\sqrt{\mathrm{var}[S_{OCT}]}} \propto \frac{\sum_{i=1}^{N} u_i}{\sqrt{\sum_{i=1}^{N} u_i^2}}, \quad (2)$$

where $u_i$ is the amplitude of the demodulated OCT signal at a spatial location, and $N = 2m - 1$. In the case of $m=2$, $N=3$ images are obtained and the relationships between the amplitudes of the ACPE OCT subimages are $S1_{OCT} = S3_{OCT} = \frac{1}{4} S0_{OCT}$ and $S2_{OCT} = 2S1_{OCT} = \frac{1}{2} S0_{OCT}$. The potential SNR improvement of the compounded $m = 2$ ACPE image can then become $SNR_{ACPE} / SNR_0 = 1.63$, where $SNR_0$ is the signal to noise ratio of $S0_{OCT}$.

EXAMPLES

II. Example 1

An exemplary polarization-diverse OCT system according to the present invention can be utilized for the examplary apparatus (e.g., as shown in Fig. 1A) that implements ACPE. Using such exemplary system according to the present invention, OCT images may be acquired at 2 frames per second (e.g., 500 axial pixels x 500 transverse pixels), which may be displayed with an inverse gray-scale lookup table, and digitally archived. The optical source which can be used in such exemplary OCT system may have a center wavelength of 1310 nm and a bandwidth of 70 nm, and thus providing an axial resolution of approximately 8 μm in the tissue.

A modified hand-held galvanometer probe (e.g., the apparatus of Fig. 1A) can be inserted in the sample arm of the OCT system 5. The objective lens 50 may have a focal length of 25 mm and a numerical aperture (NA) of 0.11, providing a measured $1/e^2$ focal spot diameter of 23 μm. A square, antireflection-coated $D = 3.1$ mm BK7 glass ($n = 1.51$) (e.g., the optical glass 20, may be inserted between the optical fiber collimator and the objective lens 50 (see Fig. 1A) so that overlaps with half of the illuminating beam. With this exemplary configuration, an OCT image separation of approximately 800 μm can be achieved. When the glass plate is inserted, the spot diameter perpendicular to the glass edge may increase by a factor of two (46

μm). In the plane of the OCT image, however, the transverse resolution is likely preserved.

**III. Example 2**

A solid phantom consisting of 1% Intralipid solution and Agar can be used to measure a reduction in speckle provided by ACPE. For example, four (4) hairs can be embedded in the Intralipid-Agar gel at different transverse positions and depths. A schematic of the phantom is depicted in Fig. 2A. The corresponding OCT images with and without the BK7 glass plate are shown in Figs. 2B and 2C, respectively. ROI's labeled 1-5 represent exemplary locations where the SNR improvement by ACPE is preferably measured. The insertion of the BK7 glass plate 20 (with a 3.1 mm BK7 glass element) in the sample arm can produce three copies of the original OCT image (see Fig. 2C), with each image being acquired at a different illumination angles and separated by group delay increments of, e.g., 800 μm. The amplitudes of the signals in the top and bottom images of Fig. 2C can be approximately half of the center image ($S1_{OCT}/S2_{OCT} = S3_{OCT}/S2_{OCT} = 1{:}2$). The compounded ACPE image shown in Fig. 2D can bes obtained by incoherently averaging the three images that are shown in Fig. 2C. A substantial reduction of speckle in the compounded image can be visualized in Fig. 2D. Compared to the original OCT image, the average ACPE SNR improvement for the five regions depicted in Fig. 2B is preferably $1.54 \pm 0.12$ (mean ± standard deviation).

**IV. Example 3**

In order to demonstrate SNR improvement *in vivo*, ACPE OCT imaging can be performed on a ventral forearm of a subject. Figs. 3A and 3B shows one representative set of images. Fig. 3A shows an exemplary OCT image of the ventral forearm obtained *in vivo* prior to the insertion of the BK7 ACPE element. Visual assessment of these pictures demonstrates a qualitative improvement in the compounded ACPE image (Fig. 3B). The boundary between the epidermis (E) and dermis (D) is more clearly demarcated with ACPE as shown in Fig. 3B. In addition, horizontal structures consistent with dermal vasculature are more readily identified in the ACPE image of Fig. 3B. The SNR can be measured for the ACPE and original OCT images in Fig. 3B, providing an exemplary SNR improvement of 1.56.

The apparatus and method according to the exemplary embodiments of the present invention are provide to reduce speckle in OCT images that does not decrease the OCT frame rate and requires only minor modifications to the OCT probe. The implementation of ACPE, implements potential compromises between speckle reduction and three other OCT system parameters: a) sample arm transverse resolution, b) total reference arm path length, and c) OCT image sensitivity. In particular, for any given objective lens, ACPE may compromise the transverse resolution in one dimension by underfilling the lens aperture for each individual beamlet. In most cases, increasing the numerical aperture (NA) of the objective can compensate for this resolution loss.

Speckle averaged ACPE-OCT images can be obtained at the same rate as conventional OCT images by scanning an increased reference arm path length delay at substantially the same frequency. In order to acquire each of the individual OCT subimages, the new scan length of the ACPE-OCT system can preferably be $L(2m-1)$, where $L$ is the original scan length of the OCT system. Using phase control RSOD lines, scan ranges up to 10 mm are possible, thus enabling $m = 3$, $L = 2$ mm, and a maximum predicted SNR improvement of ~2.1.

Increasing the reference arm path length scan range while maintaining the scan rate, may increase the electronic bandwidth and decrease the sensitivity of the OCT system. Also, because ACPE splits the sample arm power into $2m - 1$ subimages, each subimage contains a fraction of the original sample arm power. When imaging a human tissue, these losses may primarily affect the penetration depth of the OCT image. Since many features of clinical relevance, such as nuclei in patients with Barrett's esophagus or macrophages in atherosclerotic plaques, may bee present at tissue surfaces, for modest $m$, the improvements in image quality provided by ACPE likely outweigh sensitivity losses. Moreover, ongoing technical developments towards more efficient interferometer designs and higher power, clinically viable OCT sources may render ACPE sensitivity losses a non-issue.

The thickness of the path length encoding optical element described herein in the above-referenced Examples (3.1 mm BK7) may not be sufficient for OCT imaging in some tissues since the provide 800 μm separation between individual subimages. Increasing the thickness of the BK7 glass to 7.7 mm may allow a path length separation of 2 mm. This thickness may be adequate for a free-space, hand-held OCT probes, but can be be problematic in small diameter, flexible catheters,

where minimizing the rigid length can be important. In order to increase the optical thickness of the path length encoding element, a higher refractive index material such as silicon ($n = 3.5$) may be used. To create a 2 mm delay with silicon, preferably approximately 1.6 mm of the material can be used. When using high refractive index glass, dispersion imbalances between the reference and sample arms should be considered. For high-resolution OCT imaging ($\Delta\lambda/\lambda > 10\%$), appropriate selection of the optical material used for path length encoding will depend on the center wavelength and bandwidth of the source.

Advantages of the exemplary embodiment of the method and apparatus according to the present invention may include the fact that the OCT frame rate is not increased, and the addition of only a single passive element in the OCT probe should be implemented. These features of ACPE make the system and and method of the present invention compatible with OCT imaging in internal organ systems in patients. While implementation of ACPE may facilitate tradeoffs between speckle reduction and system sensitivity, the problems caused by speckle noise are likely more significant for clinical diagnosis than the penetration depth of modern OCT systems, especially at 1300 nm. Since difficulties in interpreting features on the size scale of 20 μm or less is in part a result of speckle noise in OCT images, ACPE would likely significantly improve the capabilities of OCT for the diagnosis of important diseases such as, but not limited to, dysplasia and inflammation in atherosclerosis.

Although only particular exemplary embodiments of the present invention have been described in detail herein above, those skilled in the art will readily appreciate and understand that many modifications are possible in the exemplary embodiments without materially departing from the novel teachings and advantages of this invention. Accordingly, all such modifications are intended to be included within the scope of the present invention as defined in the following claims.

CLAIMS

1. An apparatus for irradiating a sample, comprising:

a) an interferometer forwarding an electromagnetic radiation; and

b) a sample arm receiving the electromagnetic radiation, the sample arm including an arrangement which facilitates a production of at least two radiations from the electromagnetic radiation so as to irradiate the sample, the arrangement being configured to delay a first radiation of the at least two radiations with respect to a second radiation of the at least two radiations.

2. The apparatus according to claim 1, further comprising:

c) a reference arm providing a further electromagnetic radiation, wherein the interferometer receives the first, second and further radiations, and forms a resultant signal based on the first, second and further radiations; and

d) a processing arrangement generating a first image based on the first radiation and a second image based on the second radiation, wherein the first and second images are different from one another.

3. The apparatus of claim 2, wherein the processing arrangement generates a further image based on the first and second images.

4. The apparatus of claim 3, wherein the further image has a noise that is smaller than a noise of the first image and a noise of the second image.

5. The apparatus according to claim 4, wherein the further image has a signal to noise ratio that is improved according to the equation:

$$SNR_{ACPE} = \frac{\langle S_{OCT} \rangle}{\sqrt{\mathrm{var}[S_{OCT}]}} \propto \frac{\sum_{i=1}^{N} u_i}{\sqrt{\sum_{i=1}^{N} u_i^2}},$$

wherein $SNR_{ACPE}$ is the signal to noise ratio, $S_{OCT}$ is an amplitude of a high-pass filtered OCT signal, $m$ is a thickness of the arrangement, $u_i$ is an amplitude of a demodulated OCT signal at a spatial location, and $N = 2m - 1$.

6. The apparatus according to claim 5, wherein m=2 and N=3 images associated with the at least two radiations are obtained.

7. The apparatus according claim 3, wherein the further image is generated based on a mathematical combination of the first and second images.

8. The apparatus according to claim 2, wherein the sample is irradiated by the first irradiation at a first angle, wherein the sample is irradiated by the second radiation at a second angle, the first and second angles different from one another.

9. The apparatus according to claim 8, wherein the first and second angle are different from one another based on the delay and at least one of a phase and a incident angle of each of the first and second radiations.

10. The apparatus according to claim 2, further comprising a detector which detects the first electromagnetic energy, and forwards the detected energy to the processing arrangement.

11. The apparatus according to claim 1, wherein the arrangement includes two sections, each being configured to delay a respective one of the first and second radiations, and wherein a delay of the first radiation is greater than a delay of the second radiation.

12. The apparatus according to claim 1, wherein the delay of a path of the first radiation compared to a path of the second radiation is at least 500μm in air.

13. The apparatus according to claim 1, wherein the delay of a path of the first radiation compared to a path of the second radiation is at least 1mm in air.

14. The apparatus according to claim 1, wherein the arrangement has a refractive index of at least 1.5.

15. The apparatus according to claim 1, wherein the arrangement has a refractive index of at least 3.0.

16. The apparatus according to claim 1, wherein the arrangement includes silicon.

17. The apparatus according to claim 1, wherein the arrangement includes an anti-reflective coating on at least one surface thereof.

18. The apparatus according to claim 1, wherein the arrangement comprises an anti-reflection-coated BK 7 glass.

19. The apparatus according to claim 16, wherein the glass has a thickness of from about 1.6 mm to about 7.7 mm.

20. The apparatus according to claim 16, wherein the glass has a refractive index of from about 1.51 to about 3.5.

21. A catheter comprising:

a) an interferometer forwarding an electromagnetic radiation; and

b) a sample arm receiving the electromagnetic radiation, the sample arm including an arrangement which facilitates a production of at least two radiations from the electromagnetic radiation so as to irradiate the sample, the arrangement being configured to delay a first radiation of the at least two radiations with respect to a second radiation of the at least two radiations.

22. A probe for optical coherence tomography imaging, comprising:

a. an interferometer forwarding an electromagnetic radiation; and

b. a sample arm receiving the electromagnetic radiation, the sample arm including an arrangement which facilitates a production of at least two

radiations from the electromagnetic radiation so as to irradiate a sample, the arrangement being configured to delay a first radiation of the at least two radiations with respect to a second radiation of the at least two radiations.

23. A method for irradiating a sample, comprising the steps of:

a. providing an electromagnetic radiation from an interferometer; and

b. in a sample arm, facilitating production of at least two radiations from the electromagnetic radiation so as to irradiate the sample, a first radiation of the at least two radiations being delayed with respect to a second radiation of the at least two radiations.

24. An apparatus for imaging, comprising:

a. a sample arm receiving an electromagnetic radiation, the sample arm including an arrangement which facilitates a production of at least two radiations from the electromagnetic radiation so as to irradiate a sample, the arrangement being configured to delay a first radiation of the at least two radiations with respect to a second radiation of the at least two radiations;

b. a device receiving the first and second radiations from the sample arm and at least one third radiation from a reference arm, wherein the first and second radiations interfere with the third radiation;

c. at least one of spectral separating unit which separates spectrum of at least one of the first, second and third radiations into frequency components; and

d. at least one detection arrangement including a plurality of detectors, each detector capable of detecting at least a portion of at least one of the frequency components.

25. An apparatus comprising:

a. at least one first arrangement providing at least one first electro-magnetic radiation to a sample arm and at least one second electro-magnetic radiation to a non-reflective reference arm, wherein a frequency of radiation

provided by the first arrangement varies over time, wherein the sample arm receives the first electromagnetic radiation, the sample arm including an arrangement which facilitates a production of at least two radiations from the electromagnetic radiation so as to irradiate a sample, the arrangement being configured to delay a first radiation of the at least two radiations with respect to a second radiation of the at least two radiations; and

b. at least one second arrangement detecting an interference between the first and second radiations generated at the sample arm and the second electro-magnetic radiations generated at the reference.

26. An apparatus comprising:

a. at least one first arrangement providing at least one first electro-magnetic radiation to a sample arm and at least one second electro-magnetic radiation to a reference arm, wherein at least one of the first and second electro-magnetic radiation has a spectrum which changes over time, the spectrum containing multiple frequencies at a particular time, wherein the sample arm receives the first electromagnetic radiation, the sample arm including an arrangement which facilitates a production of at least two radiations from the electromagnetic radiation so as to irradiate a sample, the arrangement being configured to delay a first radiation of the at least two radiations with respect to a second radiation of the at least two radiations; and

b. at least one second arrangement detecting an interference between the first and second radiations generated at the sample arm and the second electro-magnetic radiations generated at the reference.

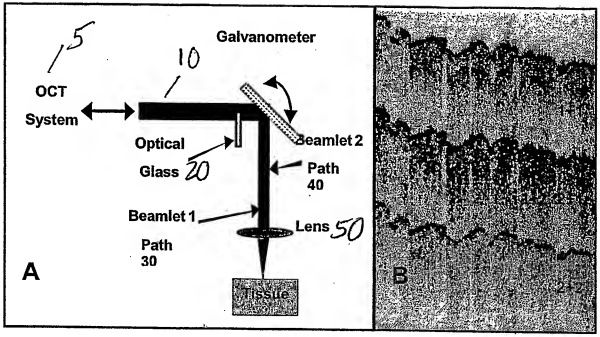

15
10
Galvanometer
OCT
System
Optical
Glass 20
Beamlet 2
Path
40
Beamlet 1
Path
30
Lens 50
A
Tissue
B

FIG. 1

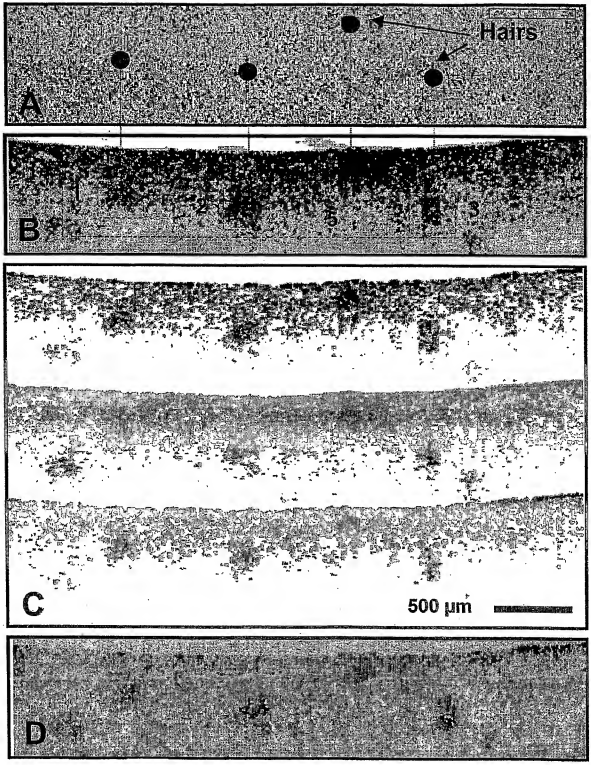



FIG. 2

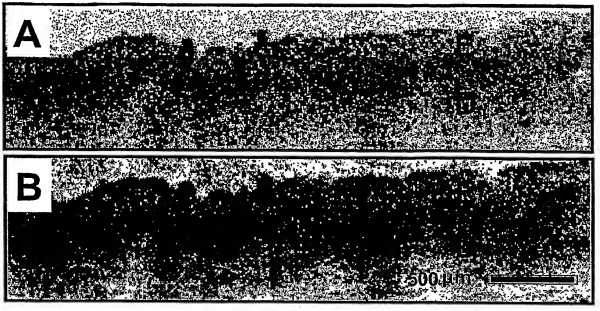



FIG. 3

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
14 October 2004 (14.10.2004)

PCT

(10) International Publication Number
WO 2004/088361 A3

(51) International Patent Classification[7]: G01B 9/02

(21) International Application Number: PCT/US2004/010152

(22) International Filing Date: 31 March 2004 (31.03.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

| | | |
|---|---|---|
| 60/459,543 | 31 March 2003 (31.03.2003) | US |
| 60/476,600 | 6 June 2003 (06.06.2003) | US |
| 60/514,769 | 27 October 2003 (27.10.2003) | US |

(71) Applicant *(for all designated States except US)*: **THE GENERAL HOSPITAL CORPORATION** [US/US]; 55 Fruit Street, Boston, MA 02114 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **TEARNEY, Guillermo, J.** [US/US]; 118 Kinnaird St., #3, Cambridge, MA 02139 (US). **IFTIMIA, Nicusor. BOUMA, Brett, E.** [US/US]; 12 Monmouth St., Quincy, MA 02171 (US).

(74) Agent: **ABELEV, Gary**; Dorsey & Whitney L.L.P., 250 Park Avenue, New York, NY 10177 (US).

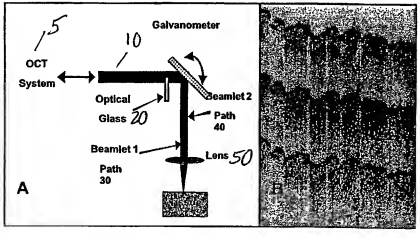
(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

**Published:**
— *with international search report*

*[Continued on next page]*

(54) Title: SPECKLE REDUCTION IN OPTICAL COHERENCE TOMOGRAPHY BY PATH LENGTH ENCODED ANGULAR COMPOUNDING




(57) Abstract: Speckle, a factor reducing image quality in optical coherence tomography ("OCT"), can limit the ability to identify cellular structures that are important for the diagnosis of a variety of diseases. The present invention allows for an implementation of an angular compounding, angular compounding by path length encoding ("ACPE") for reducing speckle in OCT images. By averaging images obtained at different incident angles, with each image encoded by path length, ACPE maintains high-speed image acquisition and implements minimal modifications to OCT probe optics. ACPE images obtained from tissue phantoms and human skin in vivo demonstrate a qualitative improvement over traditional OCT and an increased signal-to-noise ratio ("SNR"). Accordingly, apparatus probe catheter, and method are provided for irradiating a sample. In particular, an interferometer (5) may forward forwarding an electromagnetic radiation (10). In addition, a sample arm may receive the electromagnetic radiation, and can include an arrangement (20) which facilitates a production of at least two radiations (30, 40) from the electromagnetic radiation so as to irradiate the sample. Such arrangement can be configured to delay a first radiation of the at least two radiations with respect to a second radiation of the at least two radiations.

WO 2004/088361 A3

**(88) Date of publication of the international search report:**
7 April 2005

*For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/US04/10152

A. CLASSIFICATION OF SUBJECT MATTER
IPC(7) : G01B 9/02
US CL : 356/479
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 356/479, 497

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | WO 01/33820 A1 (HAAG-STREIT AG) 31 May 2001(31.5.2001), see figure 4. | 1, 11-13, 21-23, 25, 26 |
| --- | | --- |
| A | | 2-10, 14-20-, 24 |

☐ Further documents are listed in the continuation of Box C.

☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search
29 October 2004 (29.10.2004)

Date of mailing of the international search report
20 DEC 2004

Name and mailing address of the ISA/US
Mail Stop PCT, Attn: ISA/US
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
Facsimile No. (703) 305-3230

Authorized officer
for
Samuel A. Turner

Telephone No. 703-308-0956

Form PCT/ISA/210 (second sheet) (January 2004)